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13. ABSTRACT (Maximum 200) In an effort to investigate the etiology responsible for the ongoing chronic fatigue (CF) and muscle weakness in veterans with Persian Gulf (PG) illness we are performing a comprehensive evaluation of skeletal muscle in PG veterans with CF and healthy control veterans. Preliminary evaluation of 18 veterans with CF and 7 healthy control veterans shows evidence that muscle function is impaired in veterans with PG illness. Specifically, a significant decrease was found in the mitochondrial ATP producing capacity in Gulf veterans with CF compared to healthy veterans. MRI measurements show that there is no difference in the cross-sectional area of the calf muscles of both populations, indicating that the decrease in mitochondrial function of the veterans with CF is not simply the result of severe disuse or deconditioning. In addition, while the relative fatigability of skeletal muscle in the healthy veterans and veterans with CF is not different, the total amount of work that can be performed is significantly higher in the healthy veterans. Further examination of skeletal muscle using a combination of electrical stimulation, muscle biopsies and EMG is being performed to confirm the myopathic origin of chronic fatigue in PG illness.				
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FOREWORD

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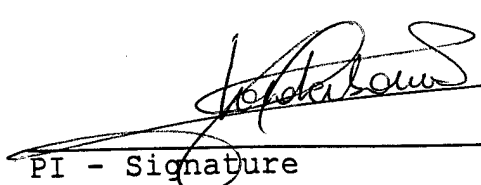
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INTRODUCTION

Since their return from the Persian Gulf region a large number of veterans have reported health problems. Even though no exact count on the prevalence of symptoms and conditions is available the VA Registry shows that about 10% of the 697,000 deployed veterans have reported chronic illnesses with a variety of symptoms, including fatigue, muscle and joint pain, headache, rashes and memory loss. In particular the musculoskeletal system seems to be frequently affected. The most recent DOD report on 18,075 veterans who completed the Comprehensive Clinical Evaluation program (CCEP) notes that 11% of the veterans report fatigue as their chief complaint, whereas a total of 47% include fatigue as one of their symptoms¹. Muscle pain is reported in 20% of the medically evaluated veterans. Similarly, the VA Registry reports fatigue in 20% of the veterans and muscle and joint pain in 1% of the veterans². Even higher incidences of fatigue and muscle pain have been reported by the English (55% tiredness, 35% muscle and joint pain)³ and the Canadian (86% fatigue, 35% muscle pain) military⁴. Thus, muscle appears to be one of the most affected systems in Persian Gulf veterans. In order to investigate the etiology of the muscle related complaints in the Persian Gulf veterans we put together an interdisciplinary group of scientists with an expertise in Biochemistry, Genetics, Muscle Physiology, Neurology, Physics and Radiology to provide a comprehensive evaluation of skeletal muscle function.

Specifically, the objective of this study is to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with Persian Gulf illness. For this purpose we are evaluating skeletal muscle function of Persian Gulf veterans with severe chronic fatigue and Persian Gulf veterans who were deployed but who have no medical problems. Our primary hypothesis is that muscle function is impaired in Persian Gulf veterans with chronic fatigue. In addition, we hypothesize that the severity of chronic fatigue in this population is related to the degree of muscle dysfunction. To test these hypotheses a battery of tests are performed. Measurements include 31P-magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), histological and biochemical analyses of muscle biopsies, electrodiagnostic evaluation of motor unit recruitment, muscle enzyme assays, isokinetic and isometric testing, and a functional status questionnaire. Complementary to the functional tests, the subjects are screened for AMP deaminase (AMPD) deficiency.

BODY

A. Subjects:

A comprehensive evaluation of skeletal muscle is performed in two subject populations: healthy Persian Gulf veterans and Persian Gulf veterans with chronic fatigue (sick). Veterans with chronic fatigue are defined as those veterans that report ongoing chronic fatigue, with an onset during or shortly after the war, in combination with muscular complaints. Muscular complaints include muscular pain (severity 3 or more on a scale of 5) and/or muscle weakness (severity 3 or more on a scale of 5). Patients are excluded from this study if they present with any other diagnosable illness. Veterans who have no medical complaints are recruited to serve as controls in this study. The control subjects are matched with the chronic fatigue veterans with regards to age and sex.

Note that we are no longer using the 1988 CDC criteria for CFS as our inclusion criteria because of the lack of Persian Gulf subjects fulfilling these requirements.

To date, 25 subjects have been studied (18 sick veterans and 7 healthy). 9 subjects were studied as part of the preliminary work and 16 as part of the currently funded work. Table 1 provides a summary of the subject's characteristics. Note that where possible data are given for all 25 subjects.

	Age	Height	Weight
Controls	28±2	70±1	180±6
Sick	33±3	68±1	181±11

Table 1. Characteristics of the healthy control PG veterans and the PG veterans with chronic fatigue (sick).

B. Isometric and isokinetic testing

Because many of the Persian Gulf veterans with chronic fatigue report exercise intolerance, prolonged fatigue after exercise and muscle weakness, we quantitatively assess the muscular strength and endurance of the ankle plantar flexors. Both measurements are performed isokinetically and isometrically. In addition, since maximum voluntary contractions rely heavily on the motivation of the subject and his or her ability to recruit and optimally fire all muscle fibers, measurements are also made using electrical stimulation.

Methods: Muscular strength and endurance of the ankle plantar flexors are tested using a Biodex electromechanical dynamometer. The subjects are seated in upright position (hip angle 90°-100°) with their back tight against the testing chair, which is firmly attached to the dynamometer. The knee joint is stabilized at 0-10° flexion. The foot is set at a 90° angle between the foot and the tibia. The following measurements are made:

1) Maximal voluntary isometric strength: defined as the highest torque of three maximal voluntary isometric contractions (MVIC) (5 sec each with 30 sec intervals).

2) Electrically evoked peak torque. Surface electrodes (bipolar 4x6 inches) are placed over the distal and proximal part of the gastrocnemius. The electrically evoked peak torque is determined using a 100 Hz tetanus (supramaximal intensity; 160ms). The highest peak torque during electrical stimulation is recorded.

3) Superimposed peak torque In order to determine the degree of central inhibition a tetanus is superimposed during the voluntary MVICs and the increase in peak torque due to stimulation recorded.

4) Maximal isokinetic strength is determined at an angular velocity of 60 degrees/sec. The subjects perform five maximal voluntary contractions and the highest peak torque is recorded.

5) Peripheral/central fatigue: To discriminate between central and peripheral fatigue we implement a modified version of the fatigue protocol described by Sharma and Miller ⁵. The subjects perform a sustained MVIC for 90 sec. Prior to and during the sustained contraction a tetanic stimuli (100Hz; supramaximal intensity; 160ms duration) is superimposed every 15 sec to verify that the muscle is fully activated. MVIC and the peak torque during the tetanic stimuli are recorded at each 15 sec interval during the exercise. The difference between the decrease in voluntary force and the decrease in force during tetanic stimulation permits the differentiation between central and peripheral (metabolic) fatigue as described by Sharma et al ⁵.

6) Maximal isokinetic endurance is tested by monitoring the maximal force during 50 repeated isokinetic plantar flexions at 60°/sec. The subjects are instructed to perform repeated plantar flexions with maximal effort. The total work and the relative decline in peak torque during the 50 contractions is recorded.

7) Twitch torque: Peak torque measured during an electrical twitch.

Results: Based on the total number of subjects that have been tested to date, the plantar flexor strength of the sick Persian Gulf veterans with chronic fatigue is significantly lower than that of the healthy veterans (Fig. 1). The largest difference was found in the isometric strength with an average peak torque of 86.6 ± 10.8 in the sick veterans ($n=18$) and 128.7 ± 11.3 ($n=7$) in the healthy veterans. An approximate 30% difference was found in the isokinetic strength at $60^\circ/\text{s}$. During superimposed electrical stimulation no increase in torque was measured in either subject population, indicating that both groups performed maximal voluntary isometric contractions. The superimposed peak torque was 124.9 ± 13.2 and 102.7 ± 14.5 , respectively ($n=16$). The smaller differences in twitch torque and tetanic torque are displayed in Fig. 1B.

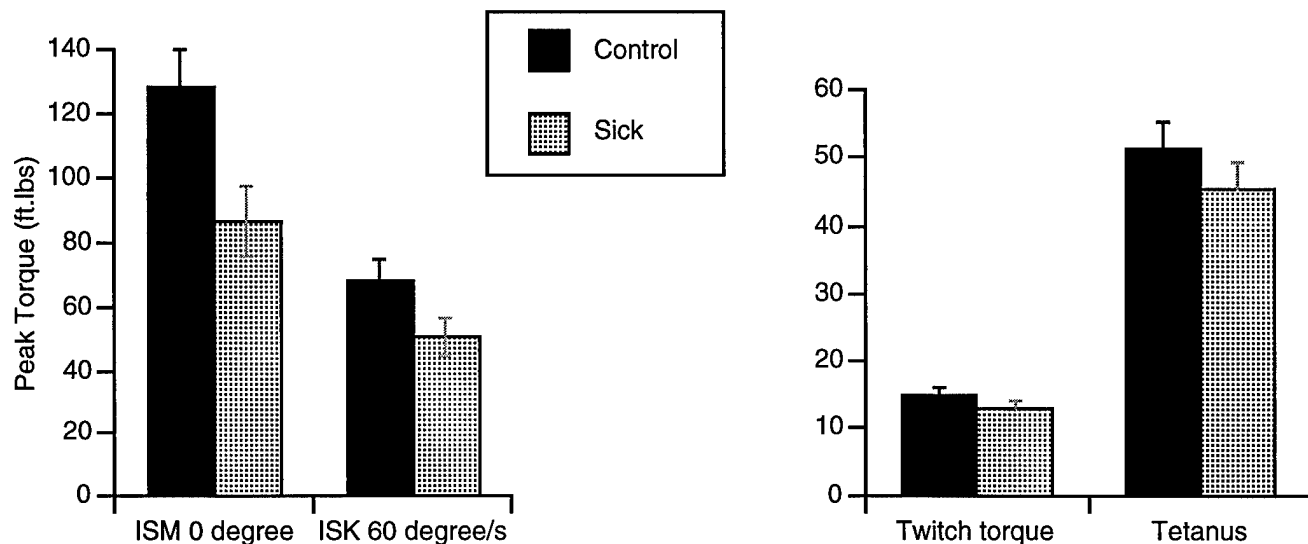


Fig. 1 Peak torque during voluntary and electrical-induced contractions in the healthy control and sick Persian Gulf veterans. ISM=isometric; ISK=isokinetic.

These preliminary data confirm the presence of muscle weakness in the Persian Gulf veterans with chronic fatigue. In addition, the superimposed electrical stimulation demonstrates that the difference in muscle strength is not due to central inhibition. No correction for differences in muscle cross-sectional area (CSA) (measured via MRI) was performed at this time. However as shown in section E, initial analysis of the MRI images shows that there is no difference between the muscle CSA of both populations.

As shown in Fig. 2 A the relative fatigability during either the isokinetic or isometric fatigue test was not higher in the sick veterans. The relative fatigue during 50 maximal isokinetic contractions was $45.0 \pm 9.1\%$ in the healthy veterans and $45.2 \pm 8.7\%$ in the sick veterans. During the isometric test we measured a higher amount of fatigue in the healthy veterans ($48.1 \pm 7.9\%$) than in the sick ($33.4 \pm 9.7\%$). Of interest to note is that based on the superimposed electrical stimulation the healthy veterans only showed 36.9% fatigue, indicating that the higher amount of fatigue measured during the voluntary isometric contraction ($48.1 \pm 7.9\%$) may have simply been due to a decrease in motivation. This was not the case in the sick veterans who showed the same degree of fatigue during electrical stimulation as during voluntary contractions.

Even though the sick veterans did not show a higher degree of relative fatigue during exercise the total amount of absolute work that was performed during 50 maximal contractions was two-fold different

(412.1±74.6J versus 795.1±124.3J) between the sick and healthy veterans, indicating a decrease in the overall exercise tolerance of veterans with chronic fatigue (Fig. 2B).

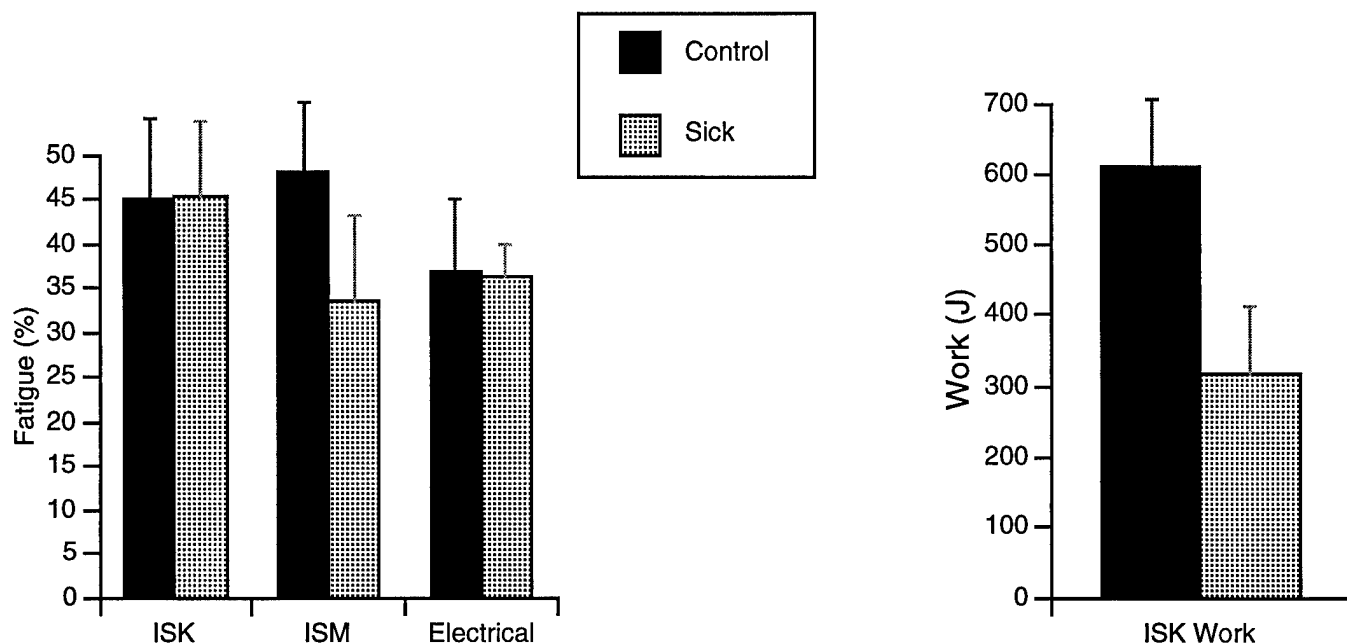


Fig. 2. A. Relative fatigability in the sick and healthy Persian Gulf veterans measured during an isometric (ISM) and Isokinetic (ISK) fatigue test as well as during superimposed electrical stimulation. (Electrical).
B. The total work performed during 50 maximal isokinetic contractions healthy Persian Gulf veterans and Persian Gulf veterans with chronic fatigue.

C. Functional testing

Methods: To determine the severity of chronic fatigue in the Persian Gulf veterans we use the Functional Status Questionnaire (FSQ) presented by Jette et al ⁷ in combination with standard functional tests. Note that both measurements have only been performed as part of this grant (not in the preliminary study).

Results: Based on the FSQ and the functional tasks the overall functional ability of the sick Persian Gulf veterans studied as part of this grant was lower than that of the healthy control veterans (Fig. 3 and 4). The sick veterans showed an overall functional score of $76.2 \pm 5.9\%$ whereas the healthy veterans scored an average of $95.5 \pm 2.0\%$ (questionnaire). The sick veterans demonstrated a 10-15% decrease in performance on functional tasks when compared to the healthy veterans.

Note that to assess the severity of chronic fatigue in our preliminary group of Persian Gulf veterans a different standardized disability questionnaire (34) was administered (n=6). Based on this questionnaire the initial group of Persian Gulf veteran showed a score of 1.27 ± 0.31 on a scoring range of 0 to 3, demonstrating a larger degree of functional impairment in our preliminary study group. The difference in severity between the veterans participating in the preliminary study and the current study is due to the fact that in this initial budget year only local veterans were recruited which were less severely affected. A special effort will be made during the

next budget year to recruit subjects from further locations who are more severely affected. A redistribution of the budget has been approved for this purpose.

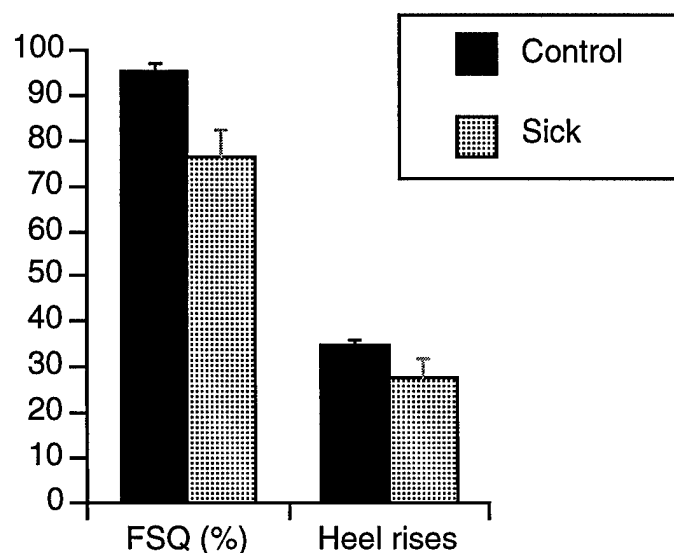


Fig. 3 Results of the functional status questionnaire (FSQ) and the heel rise test in the healthy control veterans and the veterans with chronic fatigue (sick).

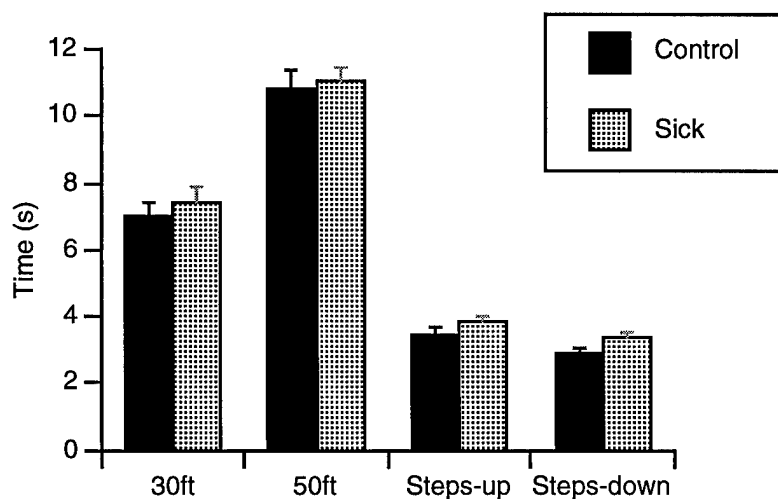


Fig. 4 Results of the timed walk and stairclimbing test in the healthy control veterans and the veterans with chronic fatigue.

D. ^{31}P -Magnetic Resonance spectroscopy (MRS)

The purpose of MRS is to assess the *in vivo* metabolic characteristics of skeletal muscle in Persian Gulf veterans with chronic fatigue. In contrast to the muscle biopsies (see below) ^{31}P -MRS is a noninvasive biochemical sampling technique which provides the opportunity to study muscle metabolism in a fully functioning system. Using this technique, we measure 1) the basal phosphate content, 2) the metabolic

compliance with exercise, 3) the *in vivo* oxidative capacity, 4) the *in vivo* ATPase flux, and 5) the *in vivo* rate of glycolysis.

Methods: All ^{31}P -MRS measurements are performed in a 1 meter, 2.0 Tesla superconducting magnet. The subjects are placed in a supine position inside the magnet with their foot positioned on a pedal ergometer operated against variable air pressure (Fig. 5).

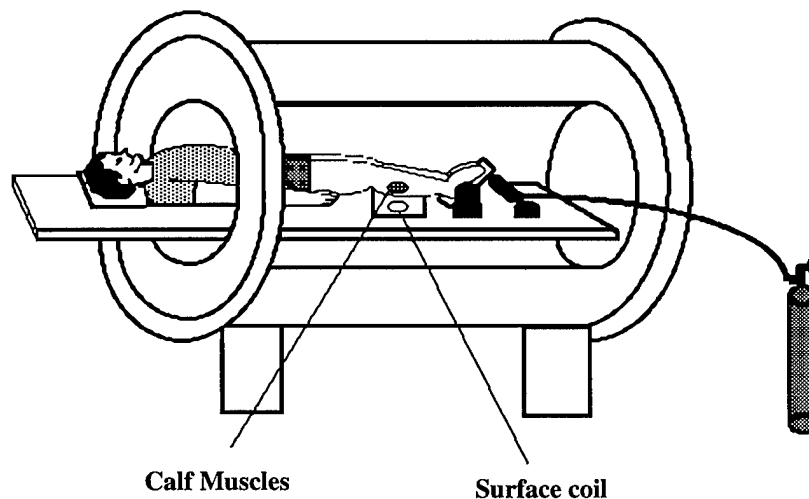


Fig. 5 Graphic display of the experimental set-up for the ^{31}P -MRS measurements.

1) Basal phosphate content: The basal content of the bioenergetically important metabolites inorganic phosphate (Pi), phosphocreatine (PCr), ATP and ADP is measured. The data are acquired over a period of 9 min, with a pulse repetition time of 30 sec.

2) Metabolic compliance with exercise: The concentration of the phosphate metabolites and the intracellular pH of skeletal muscle is measured during graded levels of exercise. The exercise consists of repeated plantar flexions, performed once every 4 sec, with the knee extended. The exercise is started at a low work load (10% Maximal Voluntary Contraction (MVC)) and the resistance is increased at the end of each minute, for a total of 5 minutes. The metabolic compliance is determined based on the relationship between the phosphate metabolite concentration, the intracellular pH and the mechanical work.

3) The *in vivo* oxidative capacity: of skeletal muscle is determined based on the rate of PCr resynthesis following a 12 seconds high repetition, "all-out" exercise protocol. Spectra are acquired with a pulse repetition time of 4 sec. The pseudo-first-order rate constant for PCr recovery (k_{PCr}) is determined by least squares fitting of the integrated PCr areas to a single exponential curve.

4) The ATPase flux / 5) Glycolysis: Since maximal rates of glycolysis and ATPase rely on the motivation of the subjects and their ability to optimally recruit all muscle fibers, both measurements are performed during voluntary and electrically-induced contractions. The voluntary exercise consists of a high repetition, "all-out" exercise of 60 sec duration. The stimulation protocol consisted of 2 min of electrically induced contractions using a 100Hz pulse train for 300 msec at supramaximal intensity. Spectra are acquired at rest (1min), during exercise and during recovery (10 min). The lactate and glycogenolytic ATP production are determined based on the pH, PCr and Pi kinetics. The ATPase flux is determined based on the rate of PCr breakdown during the first 12 sec of both voluntary and electrically induced contractions.

Results: Data acquired from the calf muscles of 25 Persian Gulf veterans show that the basal phosphate content of skeletal muscle in Persian Gulf veterans with chronic fatigue is slightly different from that of control healthy veterans. As shown in Fig. 6, a significant difference ($P<0.05$) was found between the PCr concentration of Persian Gulf veterans with chronic fatigue ($38.2\pm1.0\text{mM}$) and healthy control veterans ($42.6\pm2.0\text{mM}$). No difference was found in the Pi concentration or basal intracellular pH.

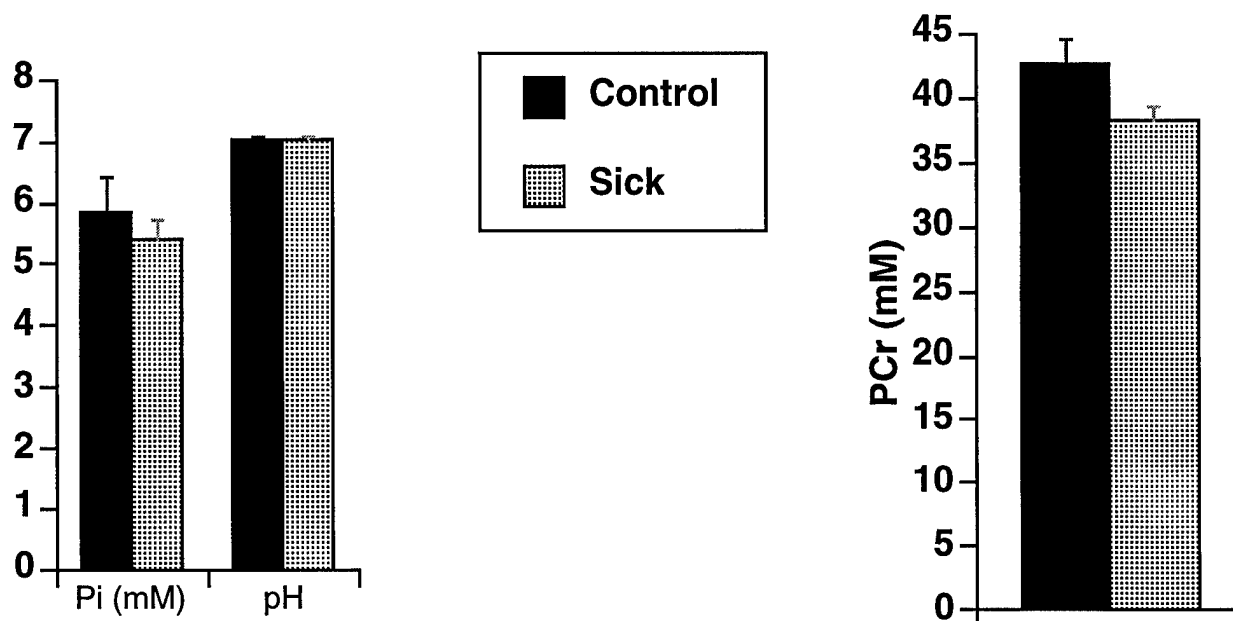


Fig. 6. Basal Pi-, PCr concentration and intracellular pH in the medial gastrocnemius of healthy veterans and veterans with chronic fatigue.

^{31}P -MRS studies performed during recovery following exercise indicate that the mitochondrial function of skeletal muscle in Persian Gulf veterans may be impaired. The rate of PCr resynthesis, a measure of the *in vivo* oxidative capacity, was significantly slower in the Persian Gulf veterans with chronic fatigue than in healthy control veterans (Fig. 7). The PCr resynthesis rate constant was $1.63\pm0.18\text{min}^{-1}$ in the veterans with chronic fatigue and $2.31\pm0.17\text{min}^{-1}$ in the healthy control veterans.

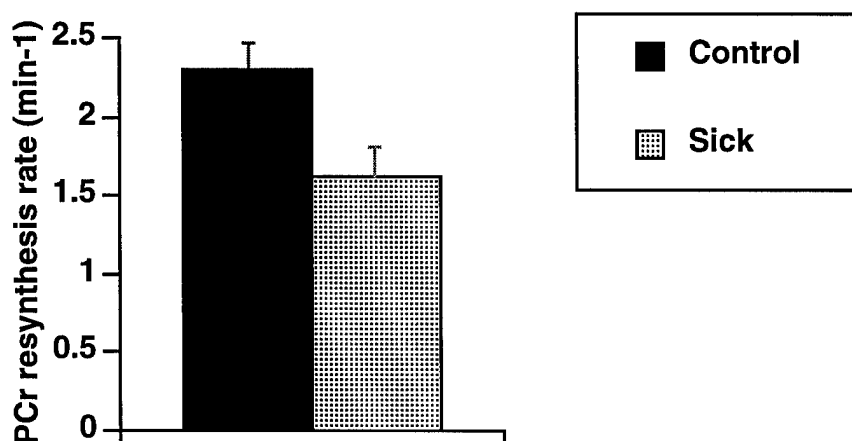


Fig. 7. PCr resynthesis rate, a measure of the *in vivo* oxidative capacity, in healthy veterans and veterans with chronic fatigue.

In order to determine the ATPase flux “all-out” exercises, requiring the veterans to perform plantar flexions as rapidly as possible, were implemented. All subjects except for one were able to perform the exercise as requested and showed rapid PCr depletion throughout exercise. Based on the changes in PCr during exercise we found that even though the ATPase flux tended to be lower in the veterans with chronic fatigue (1.92 ± 0.11 mMATP/s versus 1.62 ± 0.14), no significant difference could be measured.

E. Magnetic Resonance Imaging (MRI)

Methods: All images are collected from the right leg using a 1.5 Tesla magnet and a standard transmit and receive extremity coil. Images are collected from the patella to the calcaneus. 3D-images are acquired using a fast Gradient echo sequence (30 flip angle, TE=9msec, 256x256, FOV=16cm) for volume calculation. In addition, T2 weighted images are acquired using a TR=2,000ms and TE of 30, 60, 90 and 120msec. In order to determine differences in perfusion a method is also being implemented to perform venous plethysmography using MRI as described by ⁶. In order to increase the reliability of the MRI data analysis we have improved our segmentation program and developed a method to create T2 weighted maps of all three calf muscles (medial gastrocnemius, lateral gastrocnemius and soleus).

Results: The mean maximal cross-sectional area of the calf muscles of 3 healthy control and 3 sick Persian Gulf veterans with chronic fatigue are displayed in Table 2. Note that no difference is observed in the CSA of both subject populations, indicating that detraining or disuse is not a factor in the sick Persian Gulf veterans. The total maximal CSA was $53.9 \pm 2.7 \text{ cm}^2$ and $56.5 \pm 4.2 \text{ cm}^2$ in the healthy and sick veterans with chronic fatigue, respectively. T2 weighted maps are currently being created.

	Lateral Gastrocnemius	Medial Gastrocnemius	Soleus	Total CSA
Control	10.4 ± 0.7	14.8 ± 1.2	28.8 ± 3.4	53.9 ± 2.7
Sick	12.2 ± 0.17	17.3 ± 1.4	27.0 ± 2.8	56.5 ± 4.2

Table 2: Cross-sectional area (CSA) of the three calf muscles in the healthy and sick Persian Gulf veterans with chronic fatigue. data are expressed in cm^2 .

F. Muscle biopsies

Methods: Muscle biopsies are acquired from the medial gastrocnemius using the needle biopsy technique. In order to increase our biopsy sample size, necessary for multiple analyses, we have implemented the suction technique as described by Evans et al (8). The procedure is performed using a 60cc syringe with extension tube and a 3-way stopcock for multiple sampling. In total, 4 muscle samples are taken: 1 sample is placed in a saline solution and prepared for histological examination, 2 samples are mounted in gum tragacanth and frozen in isopentane precooled by liquid nitrogen and used for quantitative biochemical analysis of single fibers and 1 piece is cut in tiny pieces and frozen in liquid nitrogen for whole muscle homogenate biochemical analysis.

Results: To date, none of the subjects have experienced any adverse affects of the multiple sampling technique. All samples (n=16) have been stained for fiber type composition, succinic dehydrogenase activity (oxidative enzyme), α -glycerol phosphate dehydrogenase (glycolytic enzyme) and capillary density (Fig.8). Preliminary

analysis on two healthy control veterans and 1 sick veteran is shown in Table 5. The muscle biopsies of 13 subjects have also been stained for standard histological examination and were read by Dr. Shotland. The techniques for whole muscle homogenate biochemical analysis have been set up and have been validated on rabbit muscles. The samples of the veterans will be analyzed using this procedure during the next three months.

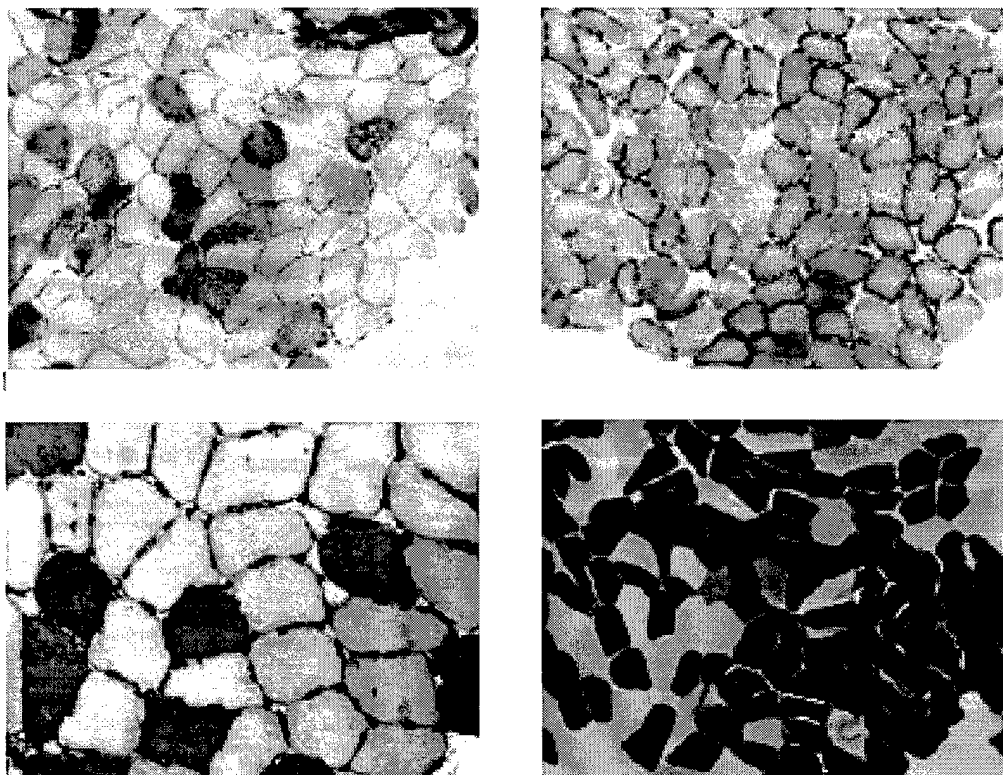


Fig. 8 Cross section of a biopsy sample of the medial gastrocnemius assayed for myofibrillar actomyosin ATPase activity (preincubation pH 4.3) (bottom right); GPD, (top left), SDH (top right) and capillar density (bottom left).

		Type I (mmol/l/min)	Type IIa (mmol/l/min)	Type IIax (mmol/l/min)
GPD				
	Control 1	0.02	0.06	0.08
	Control 2	0.03	0.06	0.12
	Sick 1	0.03	0.07	0.07
SDH				
	Control 1	0.6	0.42	0.45
	Control 2	0.91	0.8	0.64
	Sick 1	0.86	0.64	0.5

Table 3. Muscle enzyme activity in the different fiber types measured in a small sample of control and healthy veterans.

G. Muscle enzymes

Methods: Blood samples (20cc) are taken from the right arm. 5cc is sent to the lab for adolase analysis, 5cc is analyzed for CPK and LDH, 2x5cc is sent to the genetic diagnostic laboratory for DNA extraction (see below).

Results: The blood lab work has been performed on 14/16 subjects. No difference was found between sick and healthy veterans based on CPK, adolase or LDH (Table 4)

n=14	Aldolase	CPK	LDH
Control	5.8±0.8	357±151	348±79
sick	6.4±1.0	182±48	440±38

Table 4. Serum enzyme activity in healthy control veterans and veterans with chronic fatigue.

H. Electrodiagnostic evaluation

Methods: Muscle dysfunction can be related to a neuropathic as well as a myopathic process. To help in the differentiation between the two possible etiologies, needle electromyography and nerve conduction studies are performed as well as electrical stimulation (see above). A TECA Sapphire 2 channel EMG machine is used for all electrodiagnostic testing. Compound muscle action potentials are elicited from bilateral tibial and peroneal nerves. F-waves are recorded in the standard fashion at distal stimulation sites and the latencies, amplitudes and conduction velocities are calculated. Monopolar electromyography is performed on the medial gastrocnemius, lateral gastrocnemius and soleus in order to assess denervation, reinnervation and myopathic changes.

Results: The results of the nerve conduction study are given in Table 5. Based on a comparison between 6 healthy veterans and 10 veterans with chronic fatigue there was no difference in the latencies, amplitudes and conduction velocities of the tibial and peroneal nerve of both populations, indicating the absence of potential peripheral neuropathies in our veteran population.

Monopolar electromyography showed no spontaneous activity in the muscles of any of the subjects tested. However, 4/10 sick veterans had decreased interference patterns in the medial and lateral gastrocnemius and 2/10 sick veterans had decreased interference patterns in all three muscles tested. No abnormalities were noted in the interference patterns of any of the control healthy veterans. Finally, no abnormal firing rates were observed in any of the control or sick veterans.

<u>Tibial Nerve</u>						
	Conduction velocity (m/s)	F wave	Amplitude Distal (mV)	Amplitude proximal (mV)	latency proximal (ms)	latency distal (ms)
Control	51.0±1.1	50.6±1.0	7.7±0.5	6.9±0.5	13.7±0.3	5.4±0.3
Sick	51.9±1.7	50.4±1.4	7.1±0.6	6.7±0.7	13.4±0.5	5.3±0.2

Table 5. A. Results of the electrodiagnostic test performed on the tibial nerve of healthy Persian Gulf veterans and Persian Gulf veterans with chronic fatigue (sick).

Peroneal Nerve						
	Conduction velocity (m/s)	F wave	Amplitude Distal (mV)	Amplitude proximal (mV)	latency proximal (ms)	latency distal (ms)
Control	48.8±0.5	52.3±1.7	3.9±0.4	3.8±0.5	11.4±0.4	4.5±0.6
Sick	48.6±.4	50.6±1.4	4.2±0.5	4.1±0.5	11.0±0.4	4.4±0.2

Table 5. B. Results of the electrodiagnostic test performed on the peroneal nerve of healthy Persian Gulf veterans and Persian Gulf veterans with chronic fatigue (sick).

I. Genetic screening

As a complementary project to the functional studies performed in these patients, peripheral blood samples are collected for isolation of DNA. The purpose of isolating DNA is to screen for genetic defects, or polymorphisms, which may have predisposed individuals to develop symptoms following military service in the Persian Gulf. Although many genetic defects, or polymorphisms, may be responsible for the pathologic consequences experienced by the Persian Gulf veterans, and many could be screened for with the DNA samples obtained through this study, we will initially only screen for AMP deaminase (AMPD) deficiency.

Results: To date all of the samples have been labeled with random numbers not corresponding to the volunteer study number. The numbers have been stored by the biostatistician of the CRC in an encrypted format according to the new NIH-guidelines. The samples will be analyzed for AMP deaminase (AMPD) deficiency during the next 6 months.

J. Recommendations in Relation to Statement of Work Outlined in the Proposal

The first year of study has been completed. As outlined in the proposal the first 6 months served to recruit subjects and train the necessary personnel, whereas during the last 6 months we started the actual study. The training of personnel and set-up of the experiments has extremely smooth. We have acquired a great team of investigators, research staff and support staff to perform this study as proposed. In addition, the different departments involved have made the necessary facilities, resources and equipment available. We are very pleased with all aspects of the study and are confident that the study will be completed as initially proposed. Since the onset of the study we have had to make one major **adjustment** and that involved a reallocation of the budget related to subject reimbursement. Since it has been difficult to recruit a large number of subjects with severe chronic fatigue from the local area we have had to decrease the total number of subjects to be studied from 100 to 85 and increased our subject reimbursement from \$200 to \$400. The additional \$200 will allow us to fly in more **severely affected subjects from out of state**.

CONCLUSION

In an effort to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with Persian Gulf illness we are performing a comprehensive evaluation of skeletal muscle in PG veterans with chronic fatigue and healthy control veterans. To date, 25 Persian Gulf Veterans have been studied: 18 veterans with chronic fatigue and muscle weakness and 7 control healthy veterans. Even though only a small number of veterans have been studied and the data should only be considered preliminary they do indicate that muscular abnormalities may contribute to the symptom profile of Persian Gulf veterans. The most important finding in this study is a 30% decrease in the mitochondrial ATP producing capacity in Gulf veterans with chronic fatigue compared to healthy veterans. MRI measurements acquired of both populations

show that there is no difference in the cross-sectional area of the calf muscles of both populations, indicating that the decrease in mitochondrial function in veterans with chronic fatigue is not simply due to a severe degree of disuse. In addition, isokinetic and isometric testing of the plantar flexors shows a 30-50 % difference between the muscular strength of Persian Gulf veterans with chronic fatigue and healthy control veterans, which is not due to central inhibition. In contrast, the relative fatigability was not higher in the veterans with chronic fatigue. However the total absolute work that could be performed during a constant number of maximal contractions was two-fold decreased in the veterans with chronic fatigue, indicating a decrease in the overall exercise tolerance of veterans with chronic fatigue. Electrodiagnostic testing in combination with electrical stimulation show no indications of neuropathic disease in our veteran population, although a small group of veterans showed decreased interference patterns during monopolar EMG. No abnormalities in interference pattern were observed in any of the control healthy veterans. Finally, standard clinical bloodwork shows no difference in CPK, adolase and LDH in healthy control veterans and veterans with chronic fatigue. Even though these data show strong evidence of muscular abnormalities in Persian Gulf veterans with chronic fatigue further investigation will be needed to confirm the myopathic origin of the ongoing chronic fatigue and muscle weakness in Persian Gulf illness.

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